Respiratory Medicine (2012) 106, 724–729

Available online at www.sciencedirect.com

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journal homepage: www.elsevier.com/locate/rmed

Clinical characteristics and prognosis of chronic pulmonary aspergillosis

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Received 9 September 2011; accepted 31 January 2012
Available online 19 February 2012

KEYWORDS
Chronic pulmonary aspergillosis;
Chronic necrotizing pulmonary aspergillosis;
Chronic cavitary pulmonary aspergillosis

Summary
Background: The details of the clinical characteristics of patients with chronic pulmonary aspergillosis (CPA) have not been fully understood.
Method: One hundred twenty-nine consecutive patients with isolation of *Aspergillus* species by culture from respiratory specimens who attended our hospital between October 2001 and September 2009 were enrolled. Patients diagnosed with chronic pulmonary aspergillosis (CPA) were retrospectively reviewed for clinical characteristics and prognosis, compared with patients with *Aspergillus* species colonization.
Results: Forty-two (32.6%) were diagnosed with CPA, whereas 87 (67.4%) with colonization. *Aspergillus fumigatus* was significantly more frequently detected in the CPA group than in the colonization group. Regarding underlying diseases, CPA patients had a significantly higher prevalence of a history of pulmonary tuberculosis and diabetes mellitus than colonization patients. There were no significant differences between the CPA and colonization group in *Aspergillus* antigen titers. Positivity for *Aspergillus* precipitating antibody was 74.3% in CPA and 15.8% in colonization, respectively. Sensitivity and specificity of *Aspergillus* precipitating antibody for the determination of CPA was 74.4% and 84.1%, respectively.Patients with CPA had significantly shorter survival than patients with colonization (mortality rate 50.0% vs. 13.8%, observation periods: 28.7 ± 26.6 months) ($p < 0.0001$). Multivariable analysis revealed that BMI was an independent predictor of prognosis (Odds Ratio, 1.973; $p = 0.0223$).
Conclusions: CPA is a disease with a poor prognosis, which shows distinct clinical characteristics from colonization.

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doi:10.1016/j.rmed.2012.01.014

Introduction

Aspergillus species are ubiquitous, saprophytic fungi commonly found in humid soil, water, and decaying organic material of various climatic conditions. *Aspergillus* species can reach the respiratory tract by airborne transmission, causing various pulmonary diseases. Although the pathogenesis of *Aspergillus* infection has been incompletely understood, it is thought that the quantity and virulence of inhaled organisms and the adequacy of host defense are important factors for disease development. In intact host defense, namely healthy persons, the spores are eliminated by mucociliary clearance and by pulmonary macrophages and neutrophils, resulting in limitation of the proliferation and spread of *Aspergillus* organisms; however, impaired host defense by underlying pulmonary disease or decreased immune function can cause several forms of clinical conditions, including disease (i.e. pulmonary aspergillosis) and colonization.[1] Pulmonary aspergillosis is categorized into invasive aspergillosis, chronic forms of aspergillosis, and allergic forms of aspergillosis (i.e. allergic bronchopulmonary aspergillosis (ABPA)).[2] The definition of chronic pulmonary aspergillosis (CPA) has been not clearly defined and has been described with a variety of names because of a wide range of clinical, radiologic, and anatomicopathologic entities. Recently, it has been accepted that CPA mainly consists of chronic necrotizing pulmonary aspergillosis (CNPA) and chronic cavitary pulmonary aspergillosis (CCPA).[3] CNPA causes progressive destruction of the lung, while CCPA causes multiple cavities, with or without aspergilloma, accompanied by pulmonary and systemic symptoms. Although there have been many reports on invasive and allergic types, there are few reports of the chronic type. In this study, based on the isolation of *Aspergillus* species, we evaluated the clinical characteristics and prognosis of patients with CPA.

Materials and methods

Patients

We retrospectively collected consecutive patients with isolation of *Aspergillus* species by culture from respiratory specimens (sputum or samples obtained by bronchoscopy) who attended Tenryu Hospital, National Hospital Organization between October 2001 and September 2009. Respiratory specimens were cultured on potato-dextrose agar, and selected colonies were identified as *Aspergillus* by standard morphological procedures. The present study was conducted according to hospital ethics committee approval and informed consent was obtained according to the hospital's guidelines.

Diagnosis

Chronic pulmonary aspergillosis (CPA), such as chronic necrotizing pulmonary aspergillosis (CNPA) and chronic cavitary pulmonary aspergillosis (CCPA), was diagnosed according to the following criteria (4): *1)* Clinical symptoms: fever, cough, sputum production, and weight loss of 1–6 months' duration. *2)* Radiologic findings showing cavitary pulmonary lesion with evidence of paracavitary infiltrates and adjacent pleural thickening with/without fungal ball. *3*) Isolation of *Aspergillus* species by culture from sputum or samples obtained by bronchoscopy. *4*) Exclusion of similar presentations caused by active tuberculosis, other mycoses, neoplasm, abscess, Wegener's granulomatosis etc. and *5)* Exclusion of invasive pulmonary aspergillosis, allergic forms of aspergillosis, and simple aspergilloma. Colonization was defined as isolation of *Aspergillus* species with clinical or radiographic evidence that was consistent with the possibility that *Aspergillus* species were part of their flora, moreover, had neither radiological nor clinical CPA findings.[5]

Aspergillus serological examination

Aspergillus galactomannan antigen tests were performed using the platelia Aspergillus enzyme-linked immunoassay (EIA) (Bio-Rad, Marnes-la-Coquette, France). *Aspergillus* precipitating antibody tests were performed by the Ouchterlony method (Merica Diagnostics, Camberley, Surrey, UK). The $(1\rightarrow3)$ β-D glucan assay was carried out by the MK method (Seikagaku Corporation, Tokyo, Japan). Healthy volunteers free from respiratory disease were included as normal controls.

Statistical analysis

The values are expressed as the mean ± SD. For nonparametric statistical evaluation of differences between the two groups, Fisher's exact probability test or the Mann–Whitney *U* test was used. Survival was analyzed using Kaplan–Meier analysis and the log rank test. Prognostic factors were determined by univariate and multivariate analysis. Data was analysed using Statview v5.0 (SAS) software.p values < 0.05 were considered significant.

Results

Patients characteristics

The patient's characteristics are summarized in Table 1. Of 129 enrolled patients (82 males and 47 females; 73.2 ± 12.0 years old), 42 (32.6%)(31 males and 11 females; 75.1 ± 11.3 years old) were diagnosed with chronic pulmonary aspergillosis (CPA), whereas 87 (67.4%) (51 males and 36 females; 72.3 ± 12.2 years) were diagnosed with colonization. CPA patients had a significantly lower body mass index (BMI) than colonization patients (17.1 ± 2.8 vs. 20.2 ± 2.9 kg/m^2; $p < 0.0001$). Consistent with previous reports,[3,6,7] most underlying diseases were sequelae of mycobacterium such as tuberculosis and non-tuberculosis mycobacterium in both groups. CPA patients had a significantly higher prevalence of pulmonary tuberculosis (50.0 vs. 17.2%; $p = 0.0003$) and diabetes mellitus (23.8 vs. 5.7%; $p = 0.0061$) than colonization patients.

Isolation of *Aspergillus* species

As shown in Table 2, 187 *Aspergillus* species were isolated from 129 patients. Of 187 *Aspergillus* species, 90 were *Aspergillus fumigatus* (48.1%), 56 were *Aspergillus niger* (30.0%), 12 were *Aspergillus flavus* (6.4%), and 29 were